Resuscitating the macro- vs. microcirculation in septic shock

Rafael González[a,b,c,d,*], *Javier Urbano*[a,b,c,d,*] *and Jesús López-Herce*[a,b,c,d]

Purpose of review
This review summarizes current literature about the relationships between macro and microcirculation and their practical clinical implications in children with septic shock.

Recent findings
Current evidence from experimental and clinical observational studies in children and adults with septic shock reveals that the response to treatment and resuscitation is widely variable. Furthermore, there is a loss of hemodynamic coherence, as resuscitation-induced improvement in macrocirculation (systemic hemodynamic parameters) does not necessarily result in a parallel improvement in the microcirculation. Therefore, patient-tailored monitoring is essential in order to adjust treatment requirements during resuscitation in septic shock. Optimal monitoring must integrate macrocirculation (heart rate, blood pressure, cardiac output, and ultrasound images), microcirculation (videomicroscopy parameters and capillary refill time) and cellular metabolism (lactic acid, central venous blood oxygen saturation, and difference of central venous to arterial carbon dioxide partial pressure).

Summary
There is a dire need for high-quality studies to assess the relationships between macrocirculation, microcirculation and tissue metabolism in children with septic shock. The development of reliable and readily available microcirculation and tissue perfusion biomarkers (other than lactic acid) is also necessary to improve monitoring and treatment adjustment in such patients.

Keywords
children, haemodynamic, macrocirculation, microcirculation, septic shock

Downloaded from http://journals.lww.com/co-pediatrics by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 03/23/2024

INTRODUCTION

Circulatory dysfunction is common in sepsis. Impairment of macrocirculation and microcirculation have been associated with organ failure and adverse outcomes [1▪,2,3]. Moreover, the loss of hemodynamic coherence (paired response of macro and microcirculation) is one of the causes of resuscitation failure [4–7]. These facts suggest the importance to evaluate both macro and microcirculation in sepsis.

MACROCIRCULATION

Macrocirculatory parameters as clinical signs and symptoms plus basic and advanced hemodynamic monitoring are useful to evaluate resuscitation. Two types of macrocirculatory parameters should be evaluated: those related with blood flow and those related with blood pressure (BP).

Blood flow in macrocirculation, namely cardiac output (CO), is an important component of delivery of oxygen (DO_2), along with haemoglobin concentration and oxygen saturation. CO is difficult to measure in children and its clinical evaluation is highly inaccurate [8]. If the initial response to resuscitation is ineffective, advanced haemodynamic monitoring (HM) is required and several methods can be used [9]. The point-of-care ultrasound

[a]Pediatric Intensive Care Department, Hospital General Universitario Gregorio Marañón, [b]Health Research Institute of the Gregorio Marañón Hospital, [c]Maternal and Child Public Health Department. School of Medicine, Complutense University of Madrid and [d]Primary Care Interventions to Prevent Maternal and Child Chronic Diseases of Perinatal and Development Origin Network (RICORS) RD21/0012/0011, Carlos III Health Institute, Madrid, Spain

Correspondence to Jesús López-Herce, Pediatric Intensive Care Department, Hospital General Universitario Gregorio Marañón, Dr Castelo 47, 28009 Madrid, Spain. Tel: +34652263000;
e-mail: pielvi@hotmail.com

*Rafael González and Javier Urbano worked equally and are considered the first authors.

Curr Opin Pediatr 2024, 36:000–000
DOI:10.1097/MOP.0000000000001345

1040-8703 Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

SHOUT
SHARE
IT

KEY POINTS

- Hemodynamic evaluation in children with septic shock must include and integrate macrocirculation and microcirculation parameters, as well as markers of tissue metabolism, and evaluation and treatment adjustments must be individualized and tailored according to such findings.
- The most important clinical parameters for evaluating macrocirculation in children with septic shock are heart rate, blood pressure, consciousness and urine output and to assess the tissue compartment, the most recommended biomarker is serum lactate.
- Microcirculation cannot be adequately evaluated by clinical signs or classical hemodynamic devices, but evaluation with a video microscope cannot be used at the present time as a treatment guide for children with septic shock.
- During the initial phase of septic shock, hemodynamic coherence is preserved with macrocirculatory alterations, abnormal microcirculatory perfusion and elevated lactate levels.
- In the resuscitation phase of septic shock, hemodynamic coherence between the macro- and microcirculation is lost, which can lead to excessive or insufficient resuscitation and is associated with greater morbidity and mortality.

Downloaded from http://journals.lww.com/co-pediatrics by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 03/23/2024

(POCUS) is a noninvasive yet fairly accurate method. Nevertheless, it is noncontinuous, specific skills are required to perform and understand the images, and it is an operator-dependent method. Estimating CO by ultrasound methods have been related with shock reversal time reduction in children with septic shock in a randomized clinical trial [10]. However, there is no recommendation regarding which method should be used in patients with shock [9]. On the other side, the invasive methods as transpulmonary thermodilution and transpulmonary ultrasound dilution are limited by the size of the catheter and lack of resources. The lack of evidence of benefit could be a barrier. However, two aspects should be considered. Firstly, it is very difficult to achieve evidence based on high quality studies regarding the use of invasive hemodynamic monitoring methods to recommend or withhold their use. Secondly, hemodynamic changes in septic shock could be missed by other monitoring methods. The use of advanced hemodynamic monitoring is particularly helpful in fluid management coupled with an assessment of changes in cardiac output and systemic vascular resistance.

Blood flow (Q) varies directly with perfusion pressure (P) and inversely with resistance (R), $Q = P/R$. For the systemic circulation, CO equals mean arterial pressure (MAP) – central venous pressure (CVP)/systemic vascular resistance (SVR). This relationship is important for organ perfusion, as organs need both components (flow and pressure) to ensure supply of oxygen and nutrients. BP is required to maintain organ perfusion pressure and overcome the intrinsic organ pressure. Intrinsic organ pressure is rarely available (intracranial pressure, intraabdominal pressure) and CVP may not be sufficiently accurate to infer intrinsic organ pressure. Efforts applied to achieve adequate perfusion pressure can be of benefit [11], but the latest surviving sepsis campaign (SSC) recommendations don't support a perfusion pressure threshold due to lack of data [12].

Changes in the hemodynamic status in septic shock are common. An initial impairment of vascular tone (distributive shock type) might shift to a myocardial dysfunction (cardiogenic shock type), or vice versa [13]). In the absence of POCUS or advanced hemodynamic monitoring devices, clinical monitoring as heart rate, capillary refill time (CRT), skin perfusion temperature, MAP, systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP), work of breathing and respiratory mechanics should be considered [14]. In a similar way, PP (the difference between systolic and diastolic pressure) and DBP can be useful as surrogates of stroke volume and vascular tone, respectively [15]. A narrow PP might indicate a low stroke volume, due to hypovolemia or myocardial dysfunction, and would benefit from adequate preload or inotropic agent if shock is unresolved after a fluid bolus. A high PP (more than half of the SBP) and low DBP (less than a half of the SBP), especially if tachycardia is also present might indicate low vascular tone and distributive shock and would benefit from a vasopressor agent [16]. The optimal targets of SBP and MAP are unclear. The paediatric SSC guidelines were unable to issue a target of MAP, nonetheless panellists recognized that targeting a MAP between the fifth and fiftieth centile for age, or greater, was their clinical practice recommendation, with a lower MAP target being acceptable if organ perfusion variables such as mental status, perfusion, and urine output are satisfactory [12]. In situations of very low DAP such as distributive shock and vasoplegia, MAP would better reflect the real perfusion state of organs, whereas SAP values could be within normal range, underestimating the severity of the condition. On the other hand, in settings where direct measurement of MAP is less reliable, SAP provides a reasonable alternative [12].

The prevention of fluid overload and the de-escalation phase of the management of septic shock are important, especially to avoid microcirculatory damage. The Venous Excess Ultrasound (VExUS)

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

score is a useful tool to estimate the degree of venous congestion [17▪], and to actively promote fluid removal [18].

MICROCIRCULATION

Septic shock affects microcirculation as it causes endothelial glycocalyx dysfunction, leukocyte activation, intravascular coagulation and microthrombosis causing arteriovenous shunting. These changes alter the capability of the microcirculatory network to provide adequate oxygen delivery (DO_2) to guarantee tissue oxygen consumption (VO_2) [19].

Microcirculation can be evaluated by direct visualization of microcirculatory vessels in different regions and by measuring regional blood flow [20,21].

Direct microcirculatory evaluation using videomicroscopy handheld devices has been used mainly in preclinical studies. Visualization of the sublingual microcirculatory layer allows to define several aspects of microcirculatory function [22]:

(1) Diffusion capability: reflects the number of vessels in a microcirculatory area. It is described as total vessel density (TVD).
(2) Oxygen delivery (convective capability): it is described using the proportion of vessels in which blood flow is observed (proportion of perfused vessels – PPV) and the velocity of red blood cells circulating through the evaluated area (microvascular flow index).
(3) Heterogeneity: microcirculatory conditions might be different in adjacent areas. Variability among different regions is defined using the heterogeneity index (HI).

Endothelial glycocalyx is involved in blood cell interactions at the microcirculation and modification of vascular permeability. Visual measurement of perfused boundary region (PBR), the part of the glycocalyx which allows red blood cells to penetrate, is useful to define glycocalyx degradation. An increased PBR indicates a decreased glycocalyx thickness, and it has been related with a higher risk of adverse outcomes. In septic children, thicker PBR and lower capillary density have been associated with hypoalbuminemia [23▪▪,24▪▪]. Integrity and changes in the endothelial glycocalyx can also be evaluated using serum biomarkers (Syndecan-1, heparan sulfate or hyaluronan, among others) [23▪▪,24▪▪,25].

The use of direct visualization techniques to guide resuscitation in sepsis faces several barriers despite the improvement of quality imaging devices and automated analysis tools [26,27]. The patients tongue needs to remain immobile for at least 5 s to acquire adequate quality video sequences. This fact makes the lack of cooperation of conscious children one of the main limitations of the technique. Direct visualization techniques are therefore usually limited to sedated patients [28]. The other major problem is that specific microcirculatory goals are not yet well defined [29,30▪▪,31▪–33▪,34].

Perfusion index (PI) describes the ratio between pulsatile and nonpulsatile portions of the pulse oximetry signal [35] and reflects changes in the peripheral vasomotor system. PI might identify patients at shock and evaluate treatment response. In children with septic shock, low PI values have been correlated with poor outcomes and treatment failure [36▪,37▪▪].

Measurement of the time to recover normal colour after pressure applied to the nail bed of the distal phalange of the hand or foot, or the skin of other areas such as the fingertip, the thorax or the knee is known as the capillary refilling time (CRT). CRT is easy to measure, but important variations might occur depending on the evaluated site, technique [38▪], age of the patient and room temperature or lighting [39]. Prolonged CRT is associated with worse outcomes in children [40,41▪▪] and has been proposed as a goal or target for initial resuscitation in septic shock, as it is easier and more available than lactate [42–46].

Laser Doppler [47], dynamic light scattering [48▪] and thermographic imaging have also been used to describe skin perfusion changes [49▪].

Near-infrared spectroscopy (NIRS) devices allow noninvasive measurement of regional haemoglobin oxygen saturation (rSO_2). Baseline rSO_2 values may allow to detect adverse events and identify patients at risk of poor evolution. Moreover, vascular occlusion test (VOT) using NIRS has been used to evaluate microvascular reactivity in children with sepsis [50–52]. VOT measures time to desaturation from baseline after arterial flow interruption and recovery using a sphygmomanometer cuff. VOT has been used as a surrogate measure of microcirculatory capability to adapt to situations in which tissue blood blow is impaired.

Metabolism

In normal conditions, delivery of oxygen (DO_2) exceeds the amount of oxygen needed to maintain tissue metabolism (VO_2). In sepsis, disbalance between DO_2/VO_2 occurs leading to macro and microcirculatory modifications aimed to increase DO_2 and tissue O_2 extraction to maintain aerobic metabolism (DO_2/VO_2 independency). However, when compensatory mechanisms are exceeded

Downloaded from http://journals.lww.com/co-pediatrics by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 03/23/2024

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/co-pediatrics by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 03/23/2024

and DO_2 decreases below the level in which VO_2 can be fulfilled, tissues are forced to use anaerobic metabolism (DO_2/VO_2 dependency) [53].

Several arterial and venous blood gas parameters are useful in the evaluation of systemic oxygen metabolism and microcirculatory function [53]. Venous parameters are ideally measured using a pulmonary artery catheter. However, as most paediatric patients lack such a catheter, central venous catheters placed near the right atrium are used instead. Although central and mixed venous oxygen saturation have demonstrated to be correlated, their values are not fully interchangeable, especially in septic patients [54].

To assess the balance between DO_2 and VO_2, the evaluation of central venous blood oxygen saturation ($ScvO_2$), difference between central venous to arterial carbon dioxide partial pressure (Pv-aCO_2), and blood lactate concentration could be performed at the bedside when an arterial and central venous line are placed.

Briefly, $ScvO_2$ is a surrogate of mixed venous blood oxygen saturation, especially when the tip of the catheter is placed near the right atrium. Low $ScvO_2$ is related to an unbalance between the oxygen consumption and tissue oxygen delivery and, in consequence, a higher oxygen extraction rate, which means that theoretically an increase in haemoglobin (if low), arterial blood oxygen saturation or CO would restore the balance in initial phases of resuscitation. However, regarding the effect of red blood cell transfusion most studies in septic adult patients showed DO_2 improvement but VO_2 increase is infrequent [55].

Although there is no clear evidence regarding optimal $ScvO_2$ targets in septic patients, a SvO_2 >70% has been proposed and lower target values might be considered for patients with low arterial saturation such as patients with respiratory failure or cardiac shunts. On the other hand, high $SCvO_2$ values might reflect microcirculatory shunting and impaired tissue oxygen extraction, related to adverse outcomes in septic patients [56]. It is important to identify this situation to avoid efforts to increase CO which can increase endothelial and microcirculatory damage [57].

When clinical signs of shock persist despite normal $ScvO_2$, attention must be drawn to Pv-aCO_2. Pv-aCO_2 is calculated from simultaneous central venous and peripheral arterial blood samples. Is a reliable parameter to evaluate microcirculatory disturbances and is inversely related to the venous return, and hence, to CO. When microcirculatory blood flow decreases Pv-aCO_2 increases reflecting tissue CO_2 accumulation [53]. Pv-aCO_2 lower than 6 mmHg after 6 h of resuscitation was associated with higher survival in a prospective observational study in children with septic shock [58▪▪].

The relationship between CO_2 production and O_2 consumption is evaluated using the respiratory quotient (RQ). It is usually measured using indirect calorimetry which might not be available in all settings. It can also be estimated using the ratio between venoarterial difference of CO_2 and arteriovenous difference of O_2 (Cv-aCO_2/Ca-vO_2) or its surrogate Pv-aCO_2/Ca-vO_2. Its value rises over 1.0 when anaerobic metabolism is present. Values over 1.4 have been associated with adverse outcomes but correlation with microcirculatory parameters is inconsistent [53,58▪▪].

Increased (>40–50%) O_2 extraction rate (O_2ER) has been proposed to reflect a decreased DO_2 in the early phases of shock. However, its reliability to identify microcirculatory abnormalities has been questioned [8,9].

Serum lactate increases in septic patients due to tissular hypoperfusion and hypoxia. However, other mechanisms as aerobic glycolysis are also involved. Absolute values at different timepoints and changes in serum lactate levels have used as prognostic markers during septic shock in children [10,57]. SSC guidelines suggest using trends in blood lactate levels to guide resuscitation in paediatric septic shock instead of targeting advanced hemodynamic monitoring parameters such as SvO_2 [12] (Fig. 1).

RELATIONSHIP BETWEEN MACRO AND MICROCIRCULATION

Under normal physiological conditions, macrocirculation, microcirculation and tissue metabolism work coordinated to maintain the supply of oxygen to the cells. Blood flow is distributed to organs according to their oxygen demand, and microcirculatory autoregulatory mechanisms maintain tissue perfusion when changes in CO or BP occur [1▪,59].

Hemodynamic coherence (HC) exists when macrocirculation parameters are directly related to microcirculatory perfusion [60]. Both can be normal or altered, but changes in macrocirculation are accompanied by congruous changes in microcirculation [6].

In the initial phases of septic shock, hypovolemia and decreased vascular tone produce a decrease in CO and BP. In this phase, HC still exists, but tissue perfusion alterations are not homogeneous. Thus, cerebral microcirculation is usually preserved despite significant macrocirculatory alterations. At this point, increasing BP and CO with fluids and/or vasopressors will improve microcirculatory and metabolic parameters, although it is important to

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/co-pediatrics by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 03/23/2024

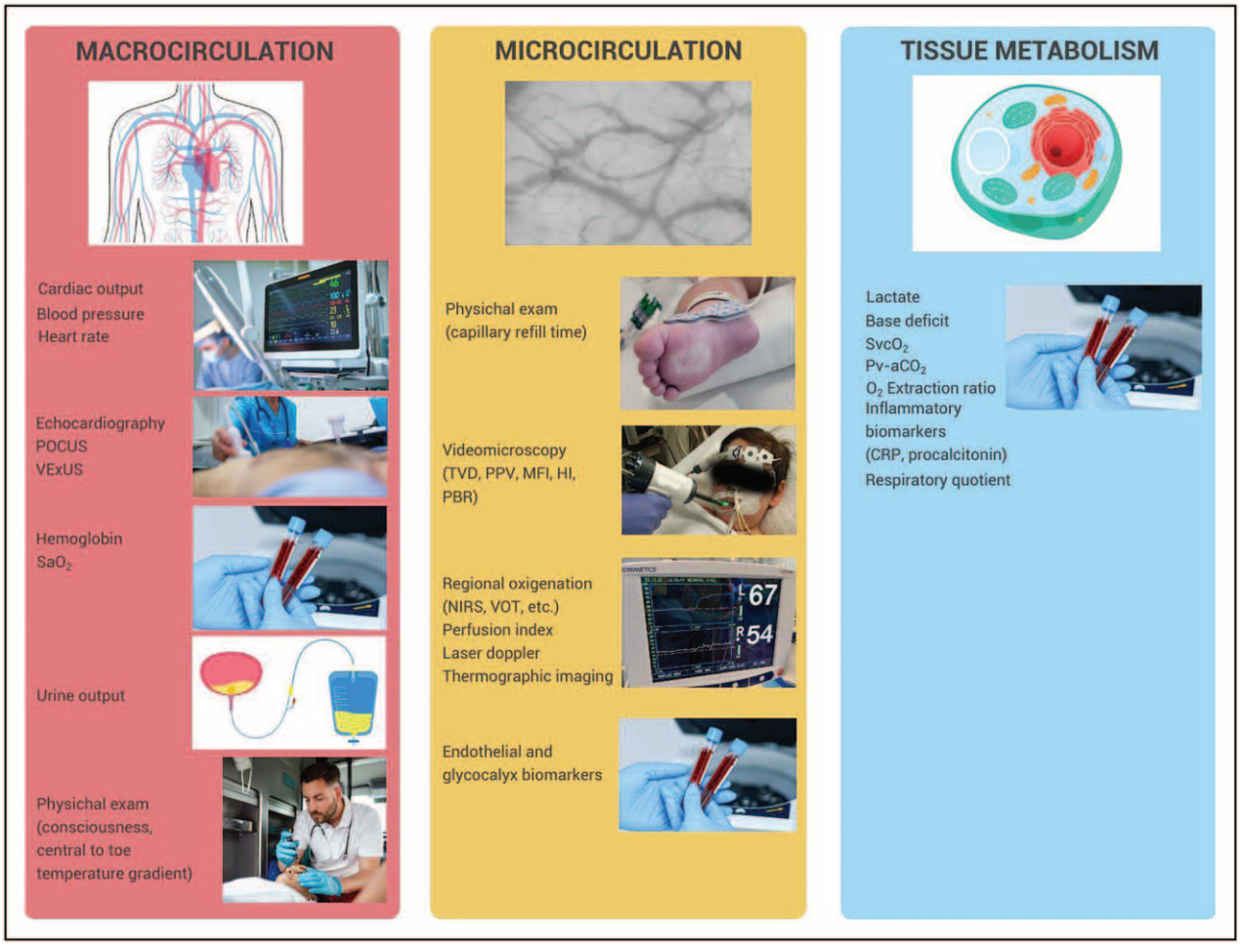

FIGURE 1. The macrocirculation, microcirculation and tissue metabolism parameters to evaluate hemodynamic and end organ perfusion.

note that the relationship between them is not linear [4].

In a later phase of septic shock, microvascular and endothelial inflammation prevail, leading to hypoperfusion and cellular hypoxia. After initial treatment, microcirculation alterations may persist even though the macrocirculation has been restored. This is called microcirculatory shock [4,7]. Table 1 summarizes the main mechanisms associated with HC loss and Table 2 the findings in the three compartments [4,5].

Experimental models

Hemodynamic coherence seems to be preserved in experimental models of septic shock. Nevertheless,

Table 1. Causes and mechanisms of haemodynamic incoherence between macro and microcirculation

Causes	Mechanisms
Heterogeneous perfusion of microcirculation	Heterogeneous capillary flow secondary to the presence of microthrombi or alterations in vasomotor tone, which decreases cellular oxygenation [40]
Capillary haematocrit haemodilution	Decreased oxygen supply and increased diffusion distance between the red blood cells and the tissue cells
Microcirculatory stasis	Produced by an increase in resistance and venous pressure that generates microcirculatory stagnation
Tissue oedema	Secondary to endothelial dysfunction, fluid administration and capillary leak that increases the diffusion distance between capillaries and tissue cells

1040-8703 Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Table 2. Types of haemodynamic incoherence [7]

Type	Alterations of the haemodynamic compartments	Parameters
Haemodynamic incoherence plus tissue hypoxia	Restored macrocirculation Impaired microcirculatory functions Cellular hypoxia	Normal BP and CO Altered perfusion Increased lactate
Haemodynamic incoherence without tissue hypoxia1	Restored macrocirculation Impaired microcirculatory functions No cellular hypoxia	Normal BP and CO Altered perfusion Normal lactate
Cellular incoherence 2	Restored macro and microcirculation Cellular oxygen altered	Normal BP Normal CO Elevated lactate

[a]Might be considered an early alarm indicator.
[b]Oxygen utilization dysfunction from mitochondrial impairment and accelerated aerobic metabolism secondary to stress. In this situation, nonhypoxic hyperlactatemia would not respond to over-resuscitation.

Downloaded from http://journals.lww.com/co-pediatrics by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 03/23/2024

resuscitation failed to completely restore microcirculatory perfusion and oxygenation [4,5,61,62].

As inferred from studies in adult patients, tissue perfusion may not respond to increments in CO in this phase of shock and fluid administration may worsen tissue oxygenation by reducing oxygen diffusion [42,63,64]. As resuscitation focuses mainly on macrocirculatory parameters, excessive or insufficient resuscitation may occur, and is associated with increased morbidity and mortality [4,7,42].

Studies in adults

Studies in adults with sepsis show a lack of HC [4] that is associated with mortality, and that the restoration of microcirculation can take a long time. The persistence of macro- and microcirculatory alterations is also associated with an increased risk of mortality [5].

Studies in children

Very few studies have assessed both macro- and microcirculation in children with sepsis [65▪]. Paize *et al.* found microcirculatory alterations despite a normal CO in children with meningococcal septic shock [25], and Top *et al.* found persistent low microcirculatory vessel density in children who died from septic shock [2].

Treatment

The first objective in the treatment of septic shock is to restore CO, oxygen transport and organ perfusion pressure to improve microcirculatory perfusion and cellular oxygen metabolism [7].

Several studies in adults with septic shock have found that correction of macrocirculation with fluids did not restore microcirculation or lactate [5]. Treatments have a variable effect on microcirculation that may depend on the timing of the intervention and the state of microcirculation, and the effects on microcirculation cannot be predicted by their macrocirculatory effects [1▪]. Fluids improve microvascular perfusion within the first 12 to 24 h of sepsis, while they have a limited or even detrimental impact on microcirculatory perfusion in later stages. The improvement of microvascular perfusion is not clearly dependent on the amount of fluid administered. In experimental studies, serum albumin might preserve the glycocalyx better than crystalloids, and hypertonic sodium lactate would improve microcirculation better as well, although there are no clinical studies that support these data [1▪]. Red blood cell transfusions can improve microcirculatory alterations at the beginning, but not in all patients. The effect of vasopressors on microcirculation may depend on the blood pressure target and the dose and type of the agent itself [66].

Therefore, clinical and microcirculatory evaluation should be performed after macrocirculatory goals have been achieved [60]. Nevertheless, the benefit of restoring microcirculatory abnormalities in patients with adequate macrocirculation parameters has not been demonstrated [4]. Consequently, the prevention of microcirculatory damage is crucial.

CONCLUSION

Septic shock causes the loss of hemodynamic coherence between the macro- and microcirculation. Response to different treatment options during resuscitation is variable. Therefore, we recommend personalizing hemodynamic monitoring and treatment of septic shock by integrating parameters of macro- and microcirculation and tissue metabolism throughout every patients' clinical course. There is an urgent need for large studies that simultaneously assess macrocirculation, microcirculation and tissue metabolism parameters in children with septic

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

shock, as well as their relationship with prognosis and response to treatment.

Acknowledgements

None.

Financial support and sponsorship

None.

Authors did not receive any funding for this work.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Backer DD, Ricottilli F, Ospina-Tascón GA. Septic shock: a microcirculation
■ disease. Curr Opin Anaesthesiol 2021; 34:85–91.

This extensive review describes how microcirculatory disturbances play a key role in the pathophysiology of septic shock.

2. Top APC. Ince C, Meij N de, *et al.* Persistent low microcirculatory vessel density in nonsurvivors of sepsis in pediatric intensive care. Crit Care Med 2011; 39:8–13.
3. Backer DD, Creteur J, Preiser J-C, *et al.* Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care 2002; 166:98–104.
4. Bakker J, Ince C. Monitoring coherence between the macro and microcirculation in septic shock. Curr Opin Crit Care 2020; 26:267–272.
5. Bakker J. Lactate levels and hemodynamic coherence in acute circulatory failure. Best Pract Res Clin Anaesthesiol 2016; 30:523–530.
6. Tibboel D, Erdem Ö, Kuiper JW. Hemodynamic coherence in critically ill pediatric patients. Best Pract Res Clin Anaesthesiol 2016; 30:499–510.
7. He H-W, Long Y, Liu D-W, *et al.* Resuscitation incoherence and dynamic circulation-perfusion coupling in circulatory shock. Chin Méd J 2019; 132:1218–1227.
8. Tibby SM, Hatherill M, Marsh MJ, *et al.* Clinicians' abilities to estimate cardiac index in ventilated children and infants. Arch Dis Child 1998; 77:516–518.
9. Singh Y, Villaescusa JU, Cruz EMda, *et al.* Recommendations for hemodynamic monitoring for critically ill children—expert consensus statement issued by the cardiovascular dynamics section of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). Crit Care 2020; 24:620.
10. EL-Nawawy AA, Abdelmohsen AM, Hassouna HM. Role of echocardiography in reducing shock reversal time in pediatric septic shock: a randomized controlled trial. J Pediatr 2018; 94:31–39.
11. Davis AL, Carcillo JA, Aneja RK, *et al.* American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Crit Care Med 2017; 45:1061–1093.
12. Weiss SL, Peters MJ, Alhazzani W, *et al.* Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Pediatr Crit Care Med 2020; 21: e52–e106.
13. Deep A, Goonasekera CDA, Wang Y, *et al.* Evolution of haemodynamics and outcome of fluid-refractory septic shock in children. Intensiv Care Med 2013; 39:1602–1609.
14. Ranjit S, Kissoon N, Argent A, *et al.* Haemodynamic support for paediatric septic shock: a global perspective. Lancet Child Adolesc Heal 2023; 7:588–598.
15. Hernandez G, Messina A, Kattan E. Invasive arterial pressure monitoring: much more than mean arterial pressure! Intensiv Care Med 2022; 48:1495–1497.
16. Ranjit S, Aram G, Kissoon N, *et al.* Multimodal monitoring for hemodynamic categorization and management of pediatric septic shock. Pediatr Crit Care Med 2014; 15:e17–e26.
17. Menéndez-Suso JJ, Rodríguez-Álvarez D, Sánchez-Martín M. Feasibility and
■ utility of the venous excess ultrasound score to detect and grade central venous pressure elevation in critically ill children. J Ultrasound Med 2023; 42:211–220.

The authors of this cross-sectional study including 33 children admitted to paediatric intensive care describe how VExUS scores is a feasible and useful tool to detect venous congestion in children.

18. Natraj R, Ranjit S. BESTFIT-T3: a tiered monitoring approach to persistent/recurrent paediatric septic shock – a pilot conceptual report. Indian J Crit Care Med 2022; 26:863–870.
19. Backer DD, Cortes DO, Donadello K, *et al.* Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence 2014; 5:73–79.
20. Valeanu L, Bubenek-Turconi S-I, Ginghina C, *et al.* Hemodynamic monitoring in sepsis—a conceptual framework of macro- and microcirculatory alterations. Diagnostics 2021; 11:1559.
21. Jung C. Assessment of microcirculation in cardiogenic shock. Curr Opin Crit Care 2019; 25:410–416.
22. Ince C, Donati A, Vincent J-L, *et al.* Second consensus on the assessment of sublingual microcirculation in critically ill patients: results from a task force of the European Society of Intensive Care Medicine. Intensive Care Med 2018; 44:281–299.
23. Fernández-Sarmiento J, Hernández-Sarmiento R, Salazar MP, *et al.* The
■■ association between hypoalbuminemia and microcirculation, endothelium, and glycocalyx disorders in children with sepsis. Microcirculation 2023; 30:e12829.

In this prospective observational study including 125 paediatric patients with sepsis the occurrence of microcirculatory abnormalities and higher glycocalyx degradation was observed more frequently in those patients presenting decreased albumin levels.

24. Fernández-Sarmiento J, Molina CF, Salazar-Pelaez LM, *et al.* Biomarkers of
■■ glycocalyx injury and endothelial activation are associated with clinical outcomes in patients with sepsis: a systematic review and meta-analysis. J Intensiv Care Med 2023; 38:95–105.

17 studies involving 3,529 septic patients were included in this meta-analysis. Authors describe how those patients presenting with abnormal glycocalyx and endothelial activation markers have higher risk of worse outcomes.

25. Paize F, Sarginson R, Makwana N, *et al.* Changes in the sublingual microcirculation and endothelial adhesion molecules during the course of severe meningococcal disease treated in the paediatric intensive care unit. Intensive Care Med 2012; 38:863–871.
26. Damiani E, Carsetti A, Casarotta E, *et al.* Microcirculation-guided resuscitation in sepsis: the next frontier? Front Med 2023; 10:1212321.
27. Backer DD. Is microcirculatory assessment ready for regular use in clinical practice? Curr Opin Crit Care 2019; 25:280–284.
28. González R, Urbano J, López J, *et al.* Evaluation of sublingual microcirculation in a paediatric intensive care unit: prospective observational study about its feasibility and utility. BMC Pediatr 2017; 17:75.
29. Mok G, Hendin A, Reardon P, *et al.* Macrocirculatory and microcirculatory endpoints in sepsis resuscitation. J Intensiv Care Med 2020; 36:1385–1391.
30. Bruno RR, Wollborn J, Fengler K, *et al.* Direct assessment of microcirculation
■■ in shock: a randomized-controlled multicenter study. Intensive Care Med 2023; 49:645–655.

In this RCT with 141 adult patients with different causes of shock (22 with septic shock) the use of sublingual microcirculatory evaluation in the management of patients with different causes of shock resulted in more treatment changes but did not improve outcomes.

31. Yajnik V, Maarouf R. Sepsis and the microcirculation: the impact on outcomes.
■ Curr Opin Anaesthesiol 2022; 35:230–235.

This review describes how the use of videomicroscopy to asses sublingual microcirculation might be useful to improve outcome of patients with sepsis.

32. Merz T, Denoix N, Huber-Lang M, *et al.* Microcirculation vs. mitochondria≥-
■ what to target? Front Med (Lausanne) 2020; 7:416.

This review describes the important role of microcirculation and cellular metabolism during shock comparing different therapeutic targets.

33. Krausova V, Neumann D, Kraus J, *et al.* Sublingual microcirculation in healthy
■ pediatric population using the sidestream dark-field imaging method. Clin Hemorheol Microcirc 2023; 85:163–171.

This observational study describes normal sublingual microcirculatory values in healthy children. 40 patients between 3 and 19 years were included.

34. Sturm T, Leiblein J, Schneider-Lindner V, *et al.* Association of microcirculation, macrocirculation, and severity of illness in septic shock: a prospective observational study to identify microcirculatory targets potentially suitable for guidance of hemodynamic therapy. J Intensive Care Med 2018; 33:256–266.
35. Lima AP, Beelen P, Bakker J. Use of a peripheral perfusion index derived from the pulse oximetry signal as a noninvasive indicator of perfusion. Crit Care Med 2002; 30:1210–1213.
36. Bazaraa H, Roby S, Salah E, *et al.* Assessment of tissue perfusion using the
■ peripheral perfusion index and lactate clearance in shock in pediatric patients. Shock 2021; 56:933–938.

50 children presenting shock were included in this prospective cohort study in which perfusion index showed similar sensitivity and specificity to lactate and lactate clearance to predict outcomes.

37. VL A. Mani SK, Ghosh S. Perfusion index variations in children with septic
■■ shock: single-center observational cohort study in India. Pediatr Crit Care Med 2024; 25:47–53.

This prospective observational study evaluates the utility of Perfusion Index assessment in 112 children with septic shock admitted to PICU.

Downloaded from http://journals.lww.com/co-pediatrics by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 03/23/2024

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

38. Hansen M, Gillespie J, Riddick T, *et al.* Evaluation of electronic measurement
■ of capillary refill for Sepsis screening at ED triage. Am J Emerg Med 2023; 70:61–65.

In this observational study including 563 adult patients consulting at emergency department, an electronic medical device designed to measure CRT was useful to improve sepsis diagnosis.

39. Lamprea S, Fernández-Sarmiento J, Barrera S, *et al.* Capillary refill time in sepsis: a useful and easily accessible tool for evaluating perfusion in children. Front Pediatr 2022; 10:1035567.
40. Fleming S, Gill P, Jones C, *et al.* The diagnostic value of capillary refill time for detecting serious illness in children: a systematic review and meta-analysis. PLoS ONE 2015; 10:e0138155.
41. Jacquet-Lagrèze M, Pernollet A, Kattan E, *et al.* Prognostic value of capillary
■■ refill time in adult patients: a systematic review with meta-analysis. Crit Care 2023; 27:473.

The utility of CRT to predict outcomes of adult patients is analyzed in this meta-analysis. After analyzing 23 studies including 60,656 patients capability to predict adverse outcomes is defined as poor but improves when high quality CRT measurements are performed.

42. Hernández G, Ospina-Tascón GA, Damiani LP, *et al.* Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock. JAMA 2019; 321:654.
43. Dubin A, Henriquez E, Hernández G. Monitoring peripheral perfusion and microcirculation. Curr Opin Crit Care 2018; 24:173–180.
44. Hernández G, Castro R, Bakker J. Capillary refill time: the missing link between macrocirculation and microcirculation in septic shock? J Thorac Dis 2020; 12:1127–1129.
45. Bakker J, Hernandez G. Can peripheral skin perfusion be used to assess organ perfusion and guide resuscitation interventions? Front Med 2020; 7:291.
46. Zampieri FG, Damiani LP, Bakker J, *et al.* Effects of a resuscitation strategy targeting peripheral perfusion status versus serum lactate levels among patients with septic shock. A Bayesian Reanalysis of the ANDROMEDA-SHOCK Trial. Am J Respir Crit Care Med 2019; 201:423–429.
47. Ait-Oufella H, Bourcier S, Alves M, *et al.* Alteration of skin perfusion in mottling area during septic shock. Ann Intensiv Care 2013; 3:31.
48. Gangaram-Panday NH, Nijenhuis LH te, Fine I, *et al.* A novel noninvasive
■ method of measuring microcirculatory perfusion and blood velocity in infants: a pilot study. Sci Rep 2022; 12:7459.

This prospective observational study describes the use of dynamic light scattering technology to measure regional blood flow in 31 infants admitted to NICU.

49. Ptak A, Dębiec-Bąk A, Stefańska M. Thermographic of the microcirculation in
■ healthy children aged 3–10 months as an objective and noninvasive method of assessment. Int J Environ Res Public Heal 2022; 19:16072.

This observational study describes the use of thermographic imaging to asses skin and muscle temperature changes after muscle stimulation in 22 healthy full-term infants.

50. Lee J-H, Jang Y-E, Song I-K, *et al.* Near-infrared spectroscopy and vascular occlusion test for predicting clinical outcome in pediatric cardiac patients. Pediatr Crit Care Med 2018; 19:32–39.
51. Laan ME van der, Roofthooft MTR, Fries MWA, *et al.* Multisite tissue oxygenation monitoring indicates organ-specific flow distribution and oxygen delivery related to low cardiac output in preterm infants with clinical sepsis. Pediatr Crit Care Med 2016; 17:764–771.
52. Samraj RS, Lopez-Colon D, Kerrigan M, *et al.* Thenar muscle oxygen saturation using vascular occlusion test: a novel technique to study microcirculatory abnormalities in pediatric heart failure patients. Pediatr Cardiol 2019; 40:1151–1158.
53. Wang J, Weng L, Xu J, *et al.* Blood gas analysis as a surrogate for microhemodynamic monitoring in sepsis. World J Emerg Med 2023; 14:421.
54. Kopterides P, Bonovas S, Mavrou I, *et al.* Venous oxygen saturation and lactate gradient from superior vena cava to pulmonary artery in patients with septic shock. Shock 2009; 31:561–567.
55. Napolitano LM, Kurek S, Luchette FA, *et al.* Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. Crit Care Med 2009; 37:3124–3157.
56. Textoris J, Fouché L, Wiramus S, *et al.* High central venous oxygen saturation in the latter stages of septic shock is associated with increased mortality. Crit Care 2011; 15:R176.
57. Teboul J-L. How to integrate hemodynamic variables during resuscitation of septic shock? J Intensiv Med 2023; 3:131–137.
58. El-Nawawy AA, Hassaan SM, Hassouna HM. Evaluation of venous-to-arterial
■■ carbon dioxide tension difference as a complementary parameter during pediatric septic shock resuscitation. Pediatr Emerg Care 2022; 38:201–206.

98 paediatric patients presenting with septic shock at PICU were included in this prospective observational study. A Pv-aCO2 value of <6mmHg after 6 h of treatment indicated normalization of tissue perfusion.

59. Hernández G, Teboul J-L. Is the macrocirculation really dissociated from the microcirculation in septic shock? Intensiv Care Med 2016; 42:1621–1624.
60. Hessler M, Kampmeier TG, Rehberg S. Effect of nonadrenergic vasopressors on macro- and microvascular coupling in distributive shock. Best Pr Res Clin Anaesthesiol 2016; 30:465–477.
61. Genderen MEvan, Klijn E, Lima A, *et al.* Microvascular perfusion as a target for fluid resuscitation in experimental circulatory shock. Crit Care Med 2014; 42: e96–e105.
62. Dubin A, Edul VSK, Pozo MO, *et al.* Persistent villi hypoperfusion explains intramucosal acidosis in sheep endotoxemia. Crit Care Med 2008; 36:535–542.
63. Donadello K, Vincent J-L, Backer DD, *et al.* Effects of fluids on microvascular perfusion in patients with severe sepsis. Intensive Care Med 2010; 36:949–955.
64. (LIVEN) TA-SSI and the LAICN. Hernández G, Kattan E, *et al.* Capillary refill time status could identify different clinical phenotypes among septic shock patients fulfilling Sepsis-3 criteria: a post hoc analysis of ANDROMEDA-SHOCK trial. Intensiv Care Med 2020; 46:816–818.
65. Arteaga GM, Crow S. End organ perfusion and pediatric microcirculation
■ assessment. Front Pediatr 2023; 11:1123405.

This review describes current available methods to assess tissue perfusion in pediatric patients with different conditions.

66. Morelli A, Donati A, Ertmer C, *et al.* Short-term effects of terlipressin bolus infusion on sublingual microcirculatory blood flow during septic shock. Intensive Care Med 2011; 37:963–969.

Downloaded from http://journals.lww.com/co-pediatrics by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 03/23/2024

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.